Evaluation Study of the Inclusion Complexes of Some Oxicams with 2-hydroxypropyl-β-cyclodextrin

LENUTA-MARIA SUTA[1], LAVINIA VLAIA[1]*, ADRIANA FULIAS[2], IONUT LEDETI[3], DANIEL HADARUGA[4] CONSTANTIN MIRCIOIU[5]

[1]University of Medicine and Pharmacy "Victor Babes", Faculty of Pharmacy, Department of Pharmaceutical Technology, 2 Eftimie Murgu Sq, 300041, Timisoara, Romania

[2] University of Medicine and Pharmacy "Victor Babes", Faculty of Pharmacy, Department of Analytical Chemistry, 2 Eftimie Murgu Sq, 300041, Timisoara, Romania

[3] University of Medicine and Pharmacy "Victor Babes", Faculty of Pharmacy, Department of Physical Chemistry, 2 Eftimie Murgu Sq, 300041, Timisoara, Romania

[4] Politehnica University of Timişoara, Faculty of Industrial Chemistry and Environmental Engineering, Applied Chemistry and Organic-Natural Compounds Engineering, 2 Victoriei Sq., 300006, Timişoara, Romania

[5] University of Medicine and Pharmacy "Carol Davila", Faculty of Pharmacy, Department of Applied Mathematics and Biostatistics, 6 Traian Vuia, 020956, Bucharest, Romania

Piroxicam (P), meloxicam (M) and tenoxicam (T) belong to the class of anti-inflammatory (AI) thiazines, and are characterized by low solubility in water. To increase the water solubility, inclusion complexes of piroxicam, meloxicam or tenoxicam with 2-hydroxypropyl-β-cyclodextrin (2HP-β-CD) were obtained. In order to obtain the inclusion complexes as particles of nanometric dimensions, the kneading method was used for. The obtained inclusion complexes were characterized by Scanning Electron Microscopy (SEM), for the evaluation of the crystals morphology and their approximate size, and by thermal analysis using Thermogravimetry (TG) and Differential Scanning Calorimetry (DSC). The results confirmed the inclusion of piroxicam, meloxicam and tenoxicam in the cyclodextrin cavity.

Keywords: piroxicam, meloxicam, tenoxicam, inclusion complexes, 2-hydroxypropyl-β-cyclodextrin

Cyclodextrins (CDs) are water-soluble cyclic oligosaccharides composed of α-1,4-linked D-glucopyranose units. The most commonly used form of these ring-shaped molecules are α-, β-, and γ-CDs formed by six, seven and eight glucose units, respectively. CDs are toroidal molecules with a truncated cone structure with a low polarity central void which is able to encapsulate, either partially or entirely, a wide variety of guest molecules of suitable size and shape, resulting in a stable association without formation of covalent bonds, the resultant entity being known as host–guest complex [1-3].

Although cyclodextrin molecules are capable of forming numerous hydrogen bonds with water molecules surrounding them, their solubility in water is limited, especially for β-cyclodextrin. This is believed to be due to the relatively strong bond of cyclodextrin molecules in crystal state (relatively high lattice energy). The random substitution of hydroxyl groups, and therefore the formation of amorphous mixtures of isomeric derivatives, will lead to considerable improvement in their solubility [4-6].

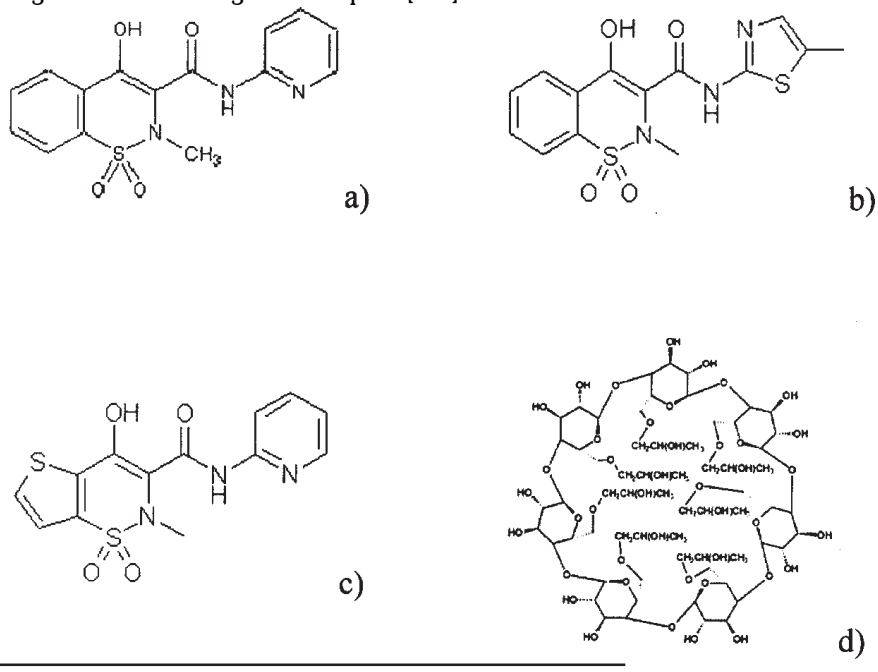

Fig. 1. Chemical structure of piroxicam (a), meloxicam (b), tenoxicam (c) and 2-hydroxypropyl-β-cyclodextrin (d)

* email: marymicumftm@yahoo.com

No.	Code	$m_{(2HP-\beta-CD)}$ (mg)	$m_{(oxicam)}$ (mg)	$Conc_{EtOH}$ (%, v/v)	$m_{complex}$ (mg)	Yield (%)
1	P_2HP-β-CD_20	395.6	84.3	20	419.1	87.33
2	M_2HP-β-CD_20	395.0	87.7	20	410.7	85.08
3	T_2HP-β-CD_20	395.5	82.7	20	415.9	86.97
4	P_2HP-β-CD_50	395.0	84.4	50	438.5	91.47
5	M_2HP-β-CD_50	395.5	87.5	50	434.0	89.86
6	T_2HP-β-CD_50	395.1	82.5	50	432.6	90.58
7	P_2HP-β-CD_96	395.7	84.6	96	412.6	85.90
8	M_2HP-β-CD_96	395.2	87.8	96	402.9	83.42
9	T_2HP-β-CD_96	395.0	82.5	96	393.9	82.49

Table 1
COMPLEXATION CONDITIONS AND YIELDS FOR THE OXICAM (P, M OR T)/2-HP-β-CD NANOPARTICLES OBTAINED. FOR ALL THE SAMPLES THE DRYING TIME WAS 6.0 h

Piroxicam, 4-hydroxy-2-methyl-N-2-pyridyl-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide, meloxicam, 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide and tenoxicam, 4-hydroxy-2-methyl-N-2-pyridyl-2H-thieno-(2,3e)-thiazine-3-carboxamide-1,2-dioxide (fig. 1) are non-steroidal anti-inflammatory drugs (NSAID), acting as preferential inhibitor of cyclooxygenase-2. Piroxicam, meloxicam and tenoxicam have demonstrated potent analgesic and anti-inflammatory activity after oral administration, being widely used in the treatment of rheumatoid arthritis and other related conditions.

Piroxicam is a weak lipophilic drug (log P=1.8), with low solubility in water (0.016 mg/mL at 25°C), meloxicam is also a weak lipophilic drug (log P=1.9), very sparingly soluble in water (0.009 mg/mL at 25°C) and tenoxicam, even more lipophilic (log P=2.4), exhibit a better solubility in water (0.076 mg/mL at 25°C) [7-9].

The aim of the present study is to evaluate the complexation of piroxicam, meloxicam and tenoxicam with 2-hydroxypropyl-β-cyclodextrin, as a possibility of increasing the solubility of these active substances in water [10, 11].

The preparation method, used to obtain the inclusion complexes of piroxicam, meloxicam and tenoxicam with cyclodextrin, was the kneading method.

The inclusion complexes obtained were characterized by Scanning Electron Microscopy (SEM), by Thermogravimetric Analysis (TG) and Differential Scanning Calorimetry (DSC) [8, 10, 12, 13].

Experimental part

Materials and methods

Piroxicam (P), meloxicam (M), tenoxicam (T) with >99% purity was a generous gift from LaborMed Pharma, (Romania), while 2-hydroxypropyl-β-CD (2HP-β-CD) was received from Cyclolab (Hungary). Ethanol and the other chemicals of analytical grades were purchased from commercial suppliers and used without further purification.

Preparation of inclusion complexes by the kneading method

Masses of cyclodextrins and piroxicam, meloxicam or tenoxicam (in a 1:1 molar ratio) were weighed, 0.5 mL of solvent, using different concentrations of ethanol (20, 50, 96%) were added and the paste obtained was cold-triturated in a mortar for 30 min, after which it was dried in the oven at 50°C to a constant mass. The precipitate obtained was dry-triturated and complexation yields were determined. Complexation yields were obtained as the ratio between the complex mass obtained and the sum of cyclodextrin and oxicam masses introduced into the process [8, 13]. The complexation conditions and yields are presented in table I.

Apparatus

The surface morphology of binary systems was examined by Scanning Electron Microscope (Inspect S50, Japan); the pictures were taken with excitation voltage of 25 kV, magnification of 3000-12000, and focusing from 10 to 14.1 mm. Thermogravimetric analysis of binary systems was performed with a NETZSCH TG 209 (Germany) model Thermogravimetric Analyzer, in range of 20-550°C, with heating rate of 10°C/min. Determinations were performed under nitrogen atmosphere.

Thermograms of binary systems were recorded on a Netzsch DSC 204 (Germany) model Differential Scanning Calorimeter, in the temperature range from 20°C to 400°C, with a heating rate of 4°C/min. Cooling was performed with liquid nitrogen, data acquisition was carried out using the Netzsch DSC 204-Acquisition Soft/2000 specific programme and the data processing was realized with the 4.0/2000 version of the Netzsch Proteus-Thermal Analysis programme [8, 13].

Results and discussions

The solution with 50% ethanol proved to be the most effective for preparation of complexes with 2HP-β-CD (table I), leading to relatively high complexation yields (91.5% for piroxicam, 89.86% for meloxicam, 90.58% for tenoxicam), compared with 96% ethanol solution, where the complexation yield was somewhat less (~83%).

Scanning Electron Microscopy (SEM) studies

The SEM analysis of 2HP-β-CD showed a less common form of crystals (polyhedral with a sphere or partial sphere appearance), with 10-20 μm in dimension (fig. 2).

In the case of inclusion complexes between piroxicam and 2-hydroxypropyl-β-cyclodextrin (P/2HP-β-CD), those prepared with 20 and 50% ethanol showed irregular crystals of dimensions up to 40μm, while those prepared with 96% ethanol appeared as rhombohedral crystal conglomerates, approximately 10μm in size. In the case of meloxicam with 2-hydroxypropyl-β-cyclodextrin (M/

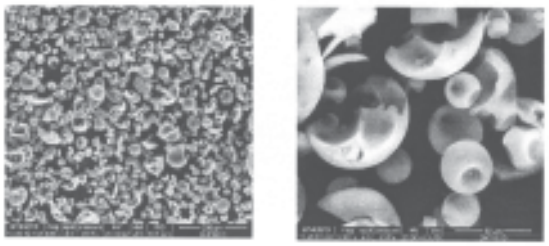

Fig. 2. SEM images for commercial 2HP-β-CD (magnification 400xand 3000x)

2HP-β-CD) complexes, the crystals were generally rhombohedral or cubic (less regulated) in shape, with dimensions varying between 10-40μm. The inclusion complexes of tenoxicam with 2-hydroxypropyl-β-cyclodextrin (T/2HP-β-CD) showed more uniform crystals in size only when they were obtained in the presence of 20 and 96% ethanol (5-40 μm, 1-10 μm respectively). For the complexes obtained in the presence of 50% ethanol, crystals had dimensions varying over a wide range (fig. 3).

Thermogravimetric analysis

The thermogravimetric profile of P/M/T/2HP-β-CD inclusion complexes are presented in figure 4.

It may be observed that all the P/2HP-β-CD inclusion complexes obtained by the kneading method, using 20, 50 and 96% ethanol, showed similar behavior when heated between 20-500°C. Water loss was between 3.2-4.1%, while the concentration of the piroxicam, released from the complex with 2-hydroxypropyl-β-cyclodextrin, was relatively low when 20 and 50% ethanol was used in the encapsulation process (0.62% and 0.67% respectively).

The thermograms of the M/2HP-β-CD inclusion complexes indicate a weight loss of 3.97-4.85% up to 100°C and of 0.48-1.9% in the interval of interest (100-300°C). In the case of these complexes, the weight loss variation with the ethanol concentration was insignificant for 20% and 50% ethanol (0.48 and 0.66% respectively), while for 96% ethanol the weight loss was significant, 1.9%. This important weight loss probably is due to the much better solubility of meloxicam in 96% ethanol, circumstance that allows a more effective achieving of the association-dissociation equilibrium, therefore a more easy formation of the complex.

Figure 4 also highlights that for T/2HP-β-CD inclusion complexes the concentration of encapsulated tenoxicam is slightly lower, only 1.76% in the presence of 96% ethanol and 0.51% and 0.72% respectively in the presence of more diluted ethanol (20 and 50% respectively). At ~210°C it turns out a more important weight loss which may be due to the release/melting/decomposition process sequences of tenoxicam, and further to the decomposition of cyclodextrin.

Differential Scanning Calorimetry analysis

The Differential Scanning Calorimetry (DSC) analysis of oxicam/2-hydroxypropyl-β-cyclodextrin (2HP-β-CD) inclusion complexes indicated that the cyclodextrin releases crystallization water in the 20-100°C interval and decomposes in the 250-350°C interval, both processes being endothermic. Between 100-250°C no energetically significant process can be observed (fig. 5).

In the figure 6 the DSC thermograms of piroxicam, meloxicam and tenoxicam complexes with 2-hydroxypropyl-β-cyclodextrin, obtained with 20, 50 and 96% ethanol are presented in comparison with the DSC thermogram of 2-hydroxypropyl-β-cyclodextrin.

In the DSC thermogram of the complex of piroxicam with 2-hydroxypropyl-β-cyclodextrin, obtained with 20% ethanol, it can be observed the release of crystallization water up to 100°C (620 J/g) and the decomposition of cyclodextrin (possibly also the releasing of piroxicam from the complex above 250°C). In the interval 110-250°C there is an endothermic peak corresponding to dissociation of the complex and to melting of piroxicam.

For the complex of piroxicam with 2-hydroxypropyl-β-cyclodextrin, obtained with 96% ethanol, the decomplexation / melting thermic effect is more

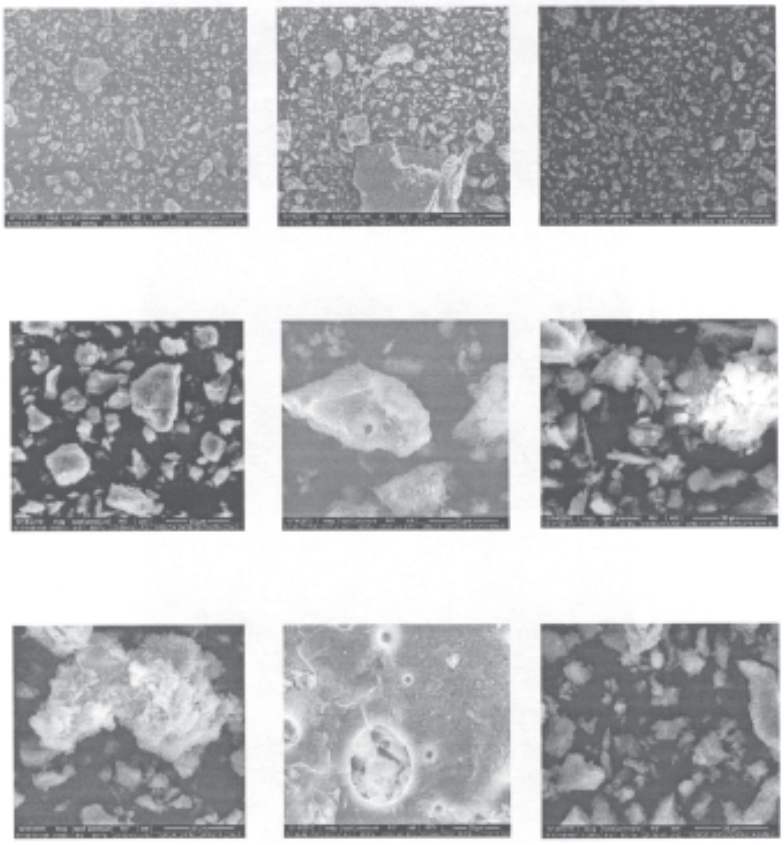

Fig. 3. SEM images of P/M/T_2HP-β-CD_20 (left), P/M/T_2HP-β-CD_50 (centre), P/M/T_2HP-β-CD_96 (right) inclusion complexes obtained by the kneading method, in the presence of 20, 50 and 96% ethanol

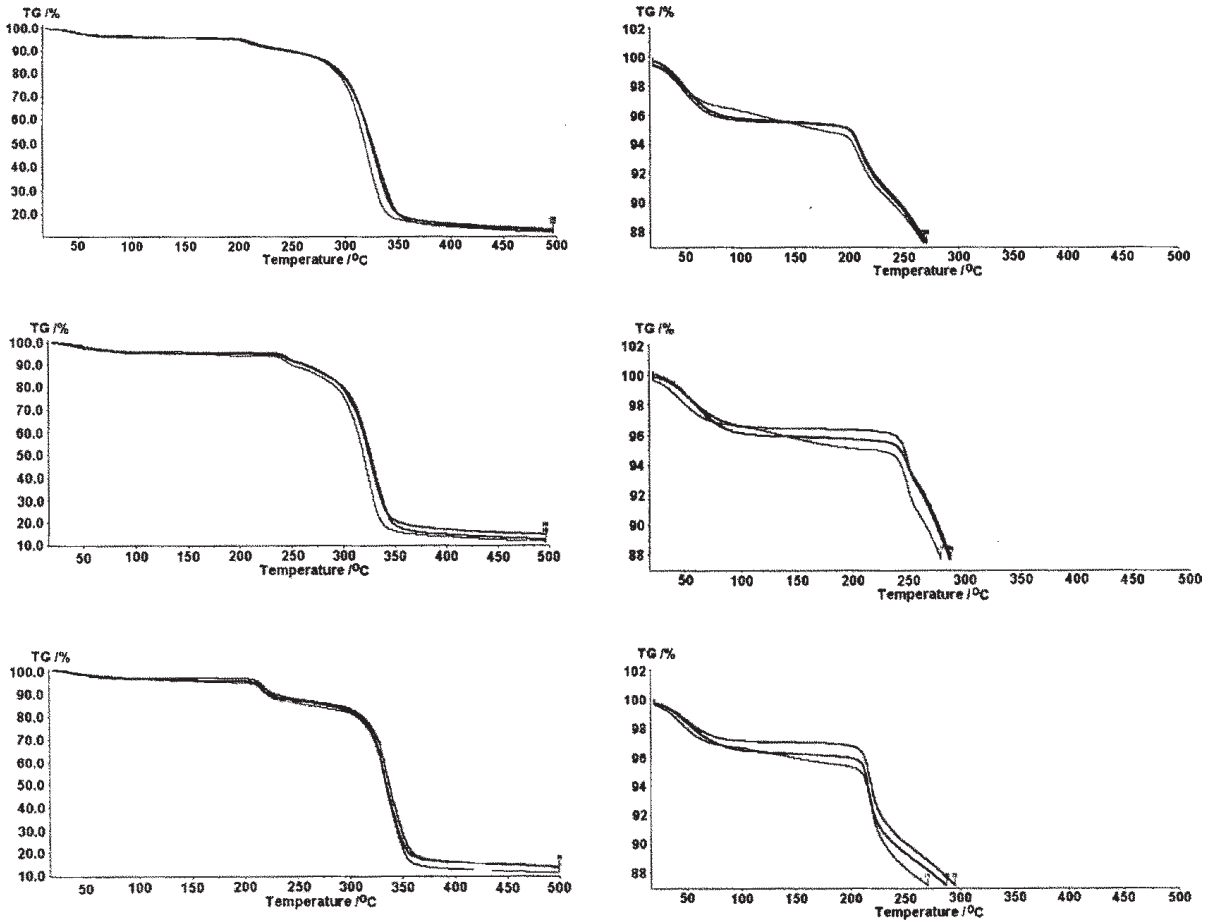

Fig. 4. Superposition of thermograms for the P/2HP-β-CD (above), M/2HP-β-CD (centre), T/2HP-β-CD (down) complexes (in the 20-500°C interval – left, and in the 20-300°C interest interval – right, respectively)

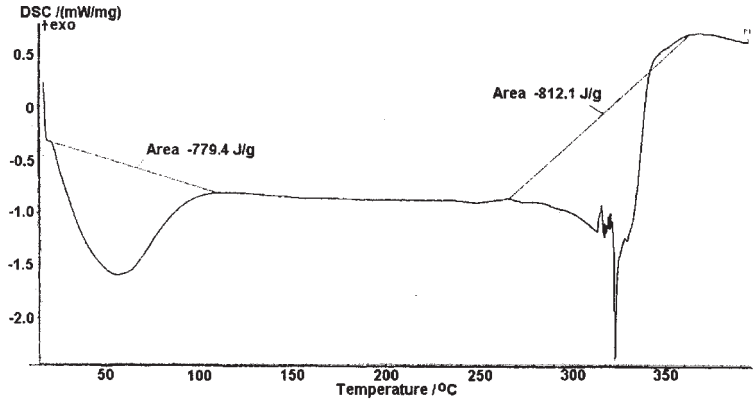

Fig. 5. DSC thermogram for 2-hydroxypropyl-β-cyclodextrin (2HP-β-CD)

significant, demonstrating a better encapsulation of the drug (244 J/g), while for crystallization water the thermic effect is lower (478 J/g). The sample obtained with 50% ethanol could not be appropriately analyzed because of its high hygroscopicity.

The DSC thermogram of meloxicam/2-hydroxypropyl-β-cyclodextrin inclusion complexes obtained with 20% and 50% ethanol (fig. 6) shows that the decomplexation/melting thermic effect in the 110-250°C interval is similar (286 J/g), while the thermic effect of dehydration is relatively low, but for the corresponding complex, obtained with 96% ethanol, the endothermic dissociation effect suggests an advanced complexation of meloxicam (320 J/g).

From the DSC thermogram of tenoxicam/2-hydroxypropyl-β-cyclodextrin complexes obtained with 20 and 96% ethanol (fig. 6), it can be easily evaluated the thermic effect of dehydration (455 J/g in both cases), but it can be also observed a peak (more difficult to evaluate) due to ~~the~~ dissociation of the complex, which appears at 120°C. In the 200-220°C interval, tenoxicam shows a structural rearrangement (exothermic effect) followed by melting/decompostion (endothermic effect). The sample obtained with 50% ethanol could not be appropriately analyzed because of its pronounced hygroscopic character.

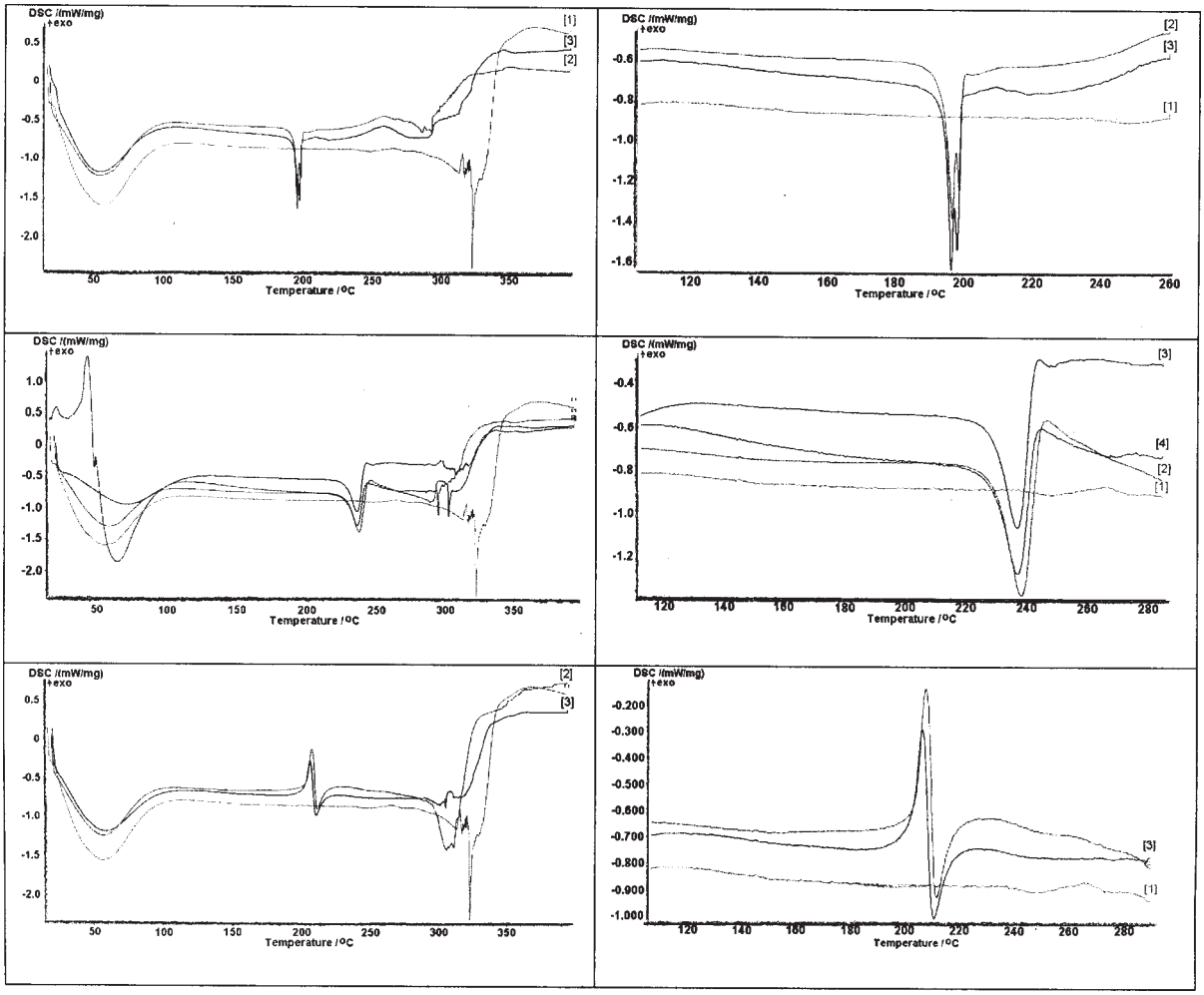

Fig. 6. Superposition of DSC thermograms for the P/2HP-β-CD (above), M/2HP-β-CD (centre) inclusion complexes and for the T/2HP-β-CD (down) inclusion complex obtained by the kneading method.

Conclusions

The oxicam/2HP-β-CD inclusion complexes were obtained with high yields by the kneading method, the highest yields (90-91.5%) being observed when 50% ethanol was used.

The thermogravimetric analysis (TG) clearly indicates the formation of inclusion complexes by kneading method, but the best results were obtained especially for meloxicam complexation in 96% ethanol.

The DSC analyses indicated the best encapsulation in the case of inclusion complexes of meloxicam with 2HP-β-CD in ethanol of 96%.

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